UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/941,492	08/29/2001	Lloyd G. Mitchell	31304-B-A-E 069906.0106	7149

21003 7590 05/05/2004

BAKER & BOTTS
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/941,492	MITCHELL ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. The election restriction requirement set forth in the previous office action is withdrawn in response to Applicant's arguments filed 10-20-03.

Priority

2. On page 1 of the specification as filed, Applicants improperly state that the filing date of provisional application number 60/008,317 is 12-15-1995. According to PTO records the filing date should state 12-07-1995.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-17 and 35-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing a chimeric mRNA in a cell *in vitro*, does not reasonably provide enablement for producing a chimeric in a cell *in vivo* for therapeutic treatment of conditions associated with papilloma virus pre-mRNA expression in a cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or

unpredictability of the art, and the breadth of the claims. *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed Cir. 1988).

The instant claims read on a cell comprising a nucleic acid wherein said nucleic acid comprises one or more target binding domains that target binding of the nucleic acid molecule to a papilloma virus pre-mRNA expressed within the cell; a 3' splice region comprising a branch point, a pyrimidine tract and a 3' splice acceptor site; a spacer region that separates the 3' splice region from the target binding domain; and a nucleotide sequence to be trans-spliced to the target pre-mRNA; wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell, and methods for producing a chimeric mRNA in a cell, wherein said cell encompasses wherein said cell is in a whole organism. The specification as filed provides only sufficient guidance and/or instruction for using the claimed nucleic acid constructs to produce chimeric mwithin a cell in an *in vitro* environment, wherein said constructs are used to produce a chimeric mRNA. However, the specification as filed does not provide sufficient guidance such that the ordinary skilled artisan could use the teachings of the specification as filed as a guide to use the compounds of the instant claims to treat conditions associated with defects in the coding region of the papilloma virus gene, in a method of gene therapy.

There are a variety of factors that complicate the gene therapy art which have not been overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of

the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, the subject it is administered to, and the disease being treated. Additionally, the specification does not provide any working examples that enable the claimed invention. Nor does the specification provide any guidance to the skilled artisan on how to make and use genetic constructs that would result in the desired effect. Even assuming that an effective genetic material is constructed, it is not evident that enough cells can be transfected to provide any therapeutic benefit.

It is noted that the instant application claims priority back to 12/15/1995, and that at the time the invention was made the state of the prior art indicated that efficient delivery and expression of foreign DNA has not yet been achieved by any method. Marshall (Science, 269:1050-1055, August, 1995) states that "there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (page 1050, column 1) and that "difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field" (page 1054, column 3). James Wilson, one skilled in the art, is quoted in the Marshall article as saying that "'[t]he actual vectors- how we're going to practice our trade- haven't been discovered yet" (page 1055, column 2).

In the instant case, the quantity of experimentation required to practice the claimed invention would encompass determining means such that all pre-trans-splicing molecules are all expressed in the same diseased cells at the same time and for a sufficient period of time such that the desired chimeric mRNA molecule is produced in a therapeutic amount to correct the defect in the diseased cells. Neither the specification as filed, nor the state of the prior art at the time the

invention was made provides any specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

Therefore, it is concluded that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention would be undue based upon the known unpredictability regarding the efficient delivery of gene therapy constructs *in vivo* and further with the production of secondary effects such as treating a disease associated with the expression of a gene, and the lack of guidance in the specification as filed in this regard. The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that the expression of a single gene is replaced and the desired secondary effect (treating a patient with a disease associated with the expression of the papilloma virus gene) is obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

5. Claims 1-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description).

Claims 1-39 are drawn to nucleic acid molecules, expression vectors and cells comprising said nucleic acid molecules, and methods for expressing said nucleic acid molecules in cells.

The nucleic acid molecules of the invention comprise one or more target binding domains that target binding of the nucleic acid molecule to a papilloma virus pre-mRNA expressed within the cell; a 3' splice region comprising a branch point, a pyrimidine tract and a 3' splice acceptor site; a spacer region that separates the 3' splice region from the target binding domain; and a nucleotide sequence to be trans-spliced to the target pre-mRNA; wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell. The specifications as filed, see Figure 48, provides the transcription map of human papillomavirus 16 (HPV-16). Additionally, Figures 52-54, provides a nucleotide sequence structural description of binding domains targeted to HPV-16 mRNA. However, the specification as filed does not teach the skilled artisan how to predict the structures of the full scope of "target binding domains" encompassed by the claims. According to the specification as filed, the papilloma virus pre-mRNAs of the invention encompass mRNAs isolated from all species of papillomavirus, including but not limited to mammalian papillomaviruses. Additionally, see page 116, paragraph [0057] which states that papillomaviruses are generally species and cell-type specific. Therefore, apart from further experimentation, the skilled artisan would not be able to predict the actual structural description of the full scope of target binding domains that target binding of the nucleic acid molecules of the invention to a papilloma virus pre-mRNA encompassed by the instant claims.

See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement. These guidelines state: "[T]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that

one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention."

Moreover, according to MPEP § 2163, which states "[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." In the instant case, the specification as filed does not provide an adequate description of the target binding domains of the invention, wherein said target binding domains target binding of the nucleic acid molecules of the invention to a papilloma virus pre-mRNA other than HPV-16 as described in the specification as filed, because papillomaviruses are both species and cell-type specific as stated by Applicants on page 116, paragraph [0057].

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claim(s) 1-39 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-39 of U.S. Patent No. 6,013487 in view of Hendricks et al. (US Patent No. 5,580,970 A). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Instant claims 1-34, and claims 1-34 of U.S. Patent No. 6,013487 are both directed to a cell comprising a nucleic acid wherein said nucleic acid comprises one or more target binding domains that target binding of the nucleic acid molecule to a target pre-mRNA expressed within the cell; a 3' splice region comprising a branch point, a pyrimidine tract and a 3' splice acceptor site; a spacer region that separates the 3' splice region from the target binding domain; and a nucleotide sequence to be trans-spliced to the target pre-mRNA; wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell, and methods for producing a chimeric mRNA in a cell, wherein said cell encompasses wherein said cell is in a whole organism. The claims of the

instant application differ from the issued claims in that claim the instant claims are specifically limited to wherein the target pre-mRNA is papilloma virus pre-mRNA.

The claims of the instant application are limited to a species of the broad class of "target pre-mRNAs" encompassed by the claims of the issued US Patent. The issued US Patent makes no mention of papilloma virus as a target pre-mRNA.

Hendricks et al. describe a variety of nucleotide sequences that are useful for the detection of human papillomavirus (HPV) mRNA or DNA is cells (see col. 3, lines 48-58). The probes and methods of Hendricks et al. allow for the detection of HPV nucleic acid in cervical cells, and a determination of a predictive value for identification of individuals at risk for progression to serious disease. According to Hendricks et al., there is a close association between HPV and cervical carcinoma (see col. 3, lines 48-55). See Figures 3-4 for a structural description of specific nucleotide sequences that are useful for binding HPV nucleic acid in cells.

It would have been obvious at the time the invention was made to design nucleic acid constructs expressed in cells according to the present invention wherein said constructs target pre-mRNA encoding papilloma virus. One of ordinary skill in the art would have been motivated to make this modification in an effort to produce potential chimeric RNA that would potentially function as therapeutics to correct defects associated with papilloma virus mRNA, and thereby further elucidate its role in the development of cervical carcinoma.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE